Polymer-based sirolimus- (Cypher) and paclitaxel-eluting (Taxus) drug eluting stents have become the treatment of choice for patients with symptomatic coronary artery disease undergoing percutaneous coronary intervention (PCI). Although these stents reduce rates of restenosis compared with bare metal stents (BMS), late thrombosis, a life threatening complication, has emerged as a major safety concern. Our understanding of the pathophysiology of late DES thrombosis is derived from animal and human pathologic samples taken after implantation of these devices. These data indicate that both DES cause substantial impairment in arterial healing characterized by lack of complete reendothelialization and persistence of fibrin when compared with BMS. This delayed healing is the primary substrate underlying all cases of late DES thrombosis at autopsy. Several additional risk factors for late stent thrombosis such as penetration of necrotic core, malapposition, overlapping stent placement, excessive stent length, and bifurcation lesions represent additional barriers to healing and should be avoided if DES are to be used to minimize the risk of late thrombosis. Because the time course of complete healing with DES in man is unknown, the optimal duration of antiplatelet treatment remains to be determined.